Remarks

The Office Action mailed November 29, 2007 has been received and reviewed. Claims 1, 12, and 22 have been amended. Claim 23 has been added. Therefore, the pending claims are claims 1-3 and 5-23. Reconsideration and withdrawal of the rejections are respectfully requested in view of the amendments and remarks provided herein.

Specification

The Examiner objected to the use of the alleged trademark BLAST, for example, at page 18. Applicant has amended the specification to give recognition to the mark BLAST, as well as other trade designation. As such, it is believed that the objection of the Examiner is overcome and withdrawal of the objection is requested.

The 35 U.S.C. §101, Rejection

The Examiner rejected claims 1-3 and 5-22 under 35 U.S.C. §101 alleging that the claimed invention is directed to non-statutory subject matter. Applicant continues to respectfully traverse the Examiner's rejection in that a useful, concrete, and tangible result is clearly presented in the claims. However, claims 1 and 12 have been amended as suggested by the Examiner (e.g., the phrase "output to a user, a display, a memory component, or another computer" was added to the claims 1 and 12).

Further, as the previous amendments to claims 1 and 12 did not overcome the Examiner's rejection under 35 U.S.C. §101, Applicants have also amended the claims to remove the language previously added to the claims by amendment in response to the previous office action (e.g., the language of original claim 4 has been reintroduced as new claim 23).

As such, it is believed that this rejection is overcome and withdrawal of the rejection is requested. Specifically, as amended in the manner suggested by the Examiner, there is clearly an actual, concrete result that is recited in the claims, and this useful result is produced in a tangible form useful to one skilled in the art.

For example, as presented in the amended claims, the present invention is a method for use in sequence data analysis. The definition of one or more PCP motifs in the multiple sequence alignment provides an actual, concrete result that is recited in the claims. Such defined PCP motifs provided as an output as set forth in the amended claims are clearly tangible and useful to one skilled in the art, e.g., for use in searching a sequence database to identify related sequence segments.

Such a task of defining one or more PCP motifs in the multiple sequence alignment and providing one or more of the defined PCP motifs as an output as set forth in the amended claims is unquestionably useful, particularly in the field of biotechnology research and development. For example, not only are the one or more defined motifs output to files (i.e., stored as part of a memory component) accessible to a user by a monitor, a printer or stored in memory or transferred to another computer, but the output files are useful to scan databases to find homologues of known structure and function and can be plotted on known 3D structures of proteins. As such, they are clearly tangible and useful outputted results.

In addition, it has been shown in subsequent work that the one or more outputted defined motifs have great value in vaccine design (see, Schein et al., Virology Journal (2005), 2:40 entitled "Stereophysicochemical variability plots highlight conserved antigenic areas in Flaviviruses"; wherein it is shown that defined PCP motifs can be used to determine the antigenically important regions of Flaviviruses, such as Dengue or West Nile, and give important information on escape mutants); and also drug design (see, Schein et al., Proteins: Structure, Function, and Bioinformatics 58:200-210 (2005) entitled "Molego-Based Definition of the Architecture and Specificity of Metal-Binding Sites"; wherein it is shown that metal binding sites of metallo-enzymes can be found by defined PCP motifs, and that the defined PCP motifs provide guidance to design inhibitors for metallo-enzymes.

These papers are attached for your convenience (they are dated after the filing of the present application, and as such, they are not prior art to the present application).

In other words, the output of the method and/or program are defined PCP motifs (e.g., a defined group of protein sequences). For example, such defined PCP motifs may be matrices of

numbers that represent the average value of each of 5 eigenvectors from the multidimensional scaling analysis of the amino acid properties at each position in the motif as described in the specification. Such outputted PCP motifs are defined, tangible and concrete, and they can be used for one or more different applications, such as scanning databases for proteins that contain similar motifs, which can be identified, for example, in a statistically significant fashion.

For at least the above reasons, it is believed that this rejection is overcome and withdrawal of the rejection is requested.

If for some reason the Examiner still does not consider the claims to be statutory subject matter, the Examiner is requested to contact Applicants' attorney identified herein to further discuss this matter and discuss any suggested amendments to move this case to issuance.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 1-3 and 5-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner questioned the clarity of the phrase "one or more of the PCP motifs" in the last element of claims 1 and 12. This language has been removed in claims 1 and 12. However, to clarify this same element in new claim 23, Applicants have amended the claims to indicate that the recitation intends to refer to "one or more of the defined PCP motifs". As such, it is believed that this rejection is overcome and withdrawal of the rejection is requested.

The 35 U.S.C. §103 Rejection

The Examiner continues to reject claims 1-3 and 5-22 under 35 U.S.C. §103(a) as being unpatentable over Venkatarajan et al. (*J. Mol. Model*, 2001; *7*:445-453) in further view of Zhu et al. (*Bioinformatics*, 2000; *16*:950-951). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. As previously presented in response to

the prior office action, the Venkatarajan reference and the Zhu reference do not describe, teach or suggest all the claim limitations.

For example, claim 1 describes a method for use in sequence data analysis that includes defining one or more PCP motifs in a multiple sequence alignment, and then providing the defined one or more PCP motifs as an output (e.g., output to a memory component such as a file to be used to search a sequence database to identify one or more related sequence segments having PCP characteristics similar to one or more of the defined PCP motifs).

The definition process to define the one or more PCP motifs which, for example, can be outputted for use in searching a sequence database, includes the first six paragraph elements of claim 1. Such elements include providing a multiple sequence alignment of a plurality of sequences (i.e., wherein the multiple sequence alignment comprises a column of aligned amino acids and/or gaps for each horizontal position of the multiple sequence alignment). A plurality of numerical physical-chemical property (PCP) descriptors for each amino acid based on a plurality of physical-chemical properties thereof are provided (i.e., wherein each of the plurality of numerical PCP descriptors corresponds to one of "N" eigenvectors used in defining the amino acids in terms of physical-chemical properties). Each amino acid in the multiple sequence alignment is described quantitatively in terms of the plurality of PCP descriptors as a series of "N" eigenvectors resulting in "N" PCP described sequence alignments, wherein each PCP described sequence alignment corresponds to and is defined with numerical PCP descriptors which correspond to one of the "N" eigenvectors (e.g., each PCP described sequence alignment comprises a plurality of columns corresponding to the columns of the multiple sequence alignment). The method further includes analyzing each of the PCP described sequence alignments, on a column by column basis, to generate conservation property data for each column, wherein the conservation property data for each column comprises an average value for the numerical PCP descriptors in the column and a standard deviation associated with the average value, and a relative entropy value for the column. The conservation property data for each of the PCP described sequence alignments is then analyzed to detect consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are

conserved based on at least the relative entropy determined for each column. One or more PCP motifs in the multiple sequence alignment are defined based at least on the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved.

It is these defined PCP motifs (i.e., quantitatively defined as recited in the claim) that may, for example, be used to search a sequence database resulting in identification of one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs, that may be plotted on known 3D structures of proteins, etc.

- Venkatarajan

The Venkatarajan reference does not describe defining PCP motifs that can be used, for example, to search a sequence database. In fact, the Venkatarajan reference only describes the derivation of the eigenvectors and the methodology for providing physicochemical properties of each amino acid in terms of 5 numbers, which represent over 200 different properties (i.e., the quantitative descriptors for the amino acids based on multidimensional scaling of physical-chemical properties as described in the Abstract of the Venkatarajan reference).

Contrary to the Examiner's allegations, there is no description, teaching or suggestion in the Venkatarajan reference that each amino acid in a multiple sequence alignment be described quantitatively in terms of the plurality of PCP descriptors as a series of "N" eigenvectors resulting in "N" PCP described sequence alignments. Further, for example, there is no description, teaching or suggestion in the Venkatarajan reference that each of the PCP described sequence alignments are analyzed, on a column by column basis, to generate conservation property data for each column, wherein the conservation property data for each column comprises an average value for the numerical PCP descriptors in the column and a standard deviation associated with the average value, and a relative entropy value for the column. Further, for example, there is no teaching or suggestion in the Venkatarajan reference that the conservation property data for each of the PCP described sequence alignments is then analyzed to detect consecutive horizontal positions of the multiple sequence alignment where the

physical-chemical properties are conserved based on at least the relative entropy determined for each column. And yet further, for example, there is no teaching or suggestion in the Venkatarajan reference that one or more PCP motifs in the multiple sequence alignment are defined based at least on the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved.

In fact, there is absolutely nothing in the Venkatarajan reference that teaches or suggests how one would quantitatively define one or more PCP motifs in a multiple sequence alignment such as described in claim 1.

Rather, the Venkatarajan reference merely states in the abstract thereof, that the "descriptors should provide a quantitative means to identify property motifs in sequences of protein families." There is nothing in Venkatarajan that provides a way of actually defining PCP motifs in a multiple sequence alignment (i.e., as is recited in the first six elements of claim 1) that can then be output.

If the Examiner believes that such elements are described therein, it is requested that the particular sections of the reference which show these elements be identified so that Applicants can appropriately respond.

- Zhu

The Examiner relies on the Zhu reference to supposedly cure the lack of teaching in the Venkatarajan reference. However, the Zhu reference does nothing to cure the deficiencies of the Venkatarajan reference.

The Zhu reference describes the MASIA program for pattern recognition in multiple aligned protein sequences. The Masia program is completely different than the present invention which defines one or more PCP motifs. Masia is nothing more than a graphics tool. In Masia:

1) the user writes a macro that indicates what pattern the user wants to detect in a given sequence alignment (or selects a pre-made macro),

2) the user makes an alignment and supplies it in a very strict format,

3) the program then scans the multiple sequence alignment and locates the pattern specified by the user.

Masia does not include code that allows one to define one or more PCP motifs in a manner as described in claim 1. Masia (i.e., the Zhu reference) describes nothing more than scanning a matrix of aligned sequences using the pre-defined macro to detect the pattern specified in the macro by the user (e.g., see, for example, the macro illustrated in Figure 1 of the Zhu reference).

In other words, Masia describes a method that looks for patterns (e.g., signatures, motifs , or characteristics) in an aligned sequence that match the defined macro. In other words, the patterns (sometimes referred to as motifs in the Zhu reference) would all match the macro.

Defining one or more PCP motifs according to the method described in claim 1 is completely different than the simple pattern recognition process of Masia. The defining of PCP motifs according to the present invention is not a pattern recognition process, but is an algorithm operable using a multiple sequence alignment that has been described in terms of a plurality of numerical PCP descriptors (e.g., PCP descriptors for each amino acid based on a plurality of physical-chemical properties thereof). The analysis performed on the multiple sequence alignment that has been described in terms of a plurality of numerical PCP descriptors (see, for example, elements 4-6 of claim 1) results in defined PCP motifs that can be very much different from one another (e.g., they do not match a specific pattern as would be the result of the Masia process).

In other words, the MASIA program is very primitive in its approach to sequence searching. The MASIA program identifies areas in aligned protein sequences that match a user defined macro or a selected macro. The MASIA program does not generate or define PCP motifs as recited in claim 1. Rather, patterns in an alignment (e.g., referred to as motifs in the Zhu reference) are identified using a preset macro for determining consensus at any conservation level. The user can alter the property library and define macros to search for the specific patterns (see Zhu, page 950, first column). In other words, macros used for searching are

directly encoded by the user, e.g., who can write a macro that defines the search criteria or use one of a series of pre-written macros at the site.

A defined PCP-motif according to the invention as described in claim 1 is completely different than a motif identified by means of scanning for a predefined pattern as is done with MASIA. A PCP motif according to the present invention as described in claim 1 is a motif in the multiple sequence alignment defined based on at least the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved according to at least one eigenvector. There is nothing in either references cited by the Examiner that teaches or suggests such a PCP motif generated based on such detection.

The methodology of MASIA consists only of being able to scan alignments in both horizontal and vertical directions for finding matches to the user created macros (or a selected macro). MASIA does not include defining PCP motifs as described in claim 1.

As such, neither of the references cited by the Examiner define PCP motifs as described in claim 1, which, for example, can then be used for other purposes, such as to search sequence databases. Venkatarajan merely provides PCP descriptors, and Zhu consists only of being able to scan alignments in both horizontal and vertical directions using user selected or encoded search macros.

- Combination of Venkatarajan and Zhu

  The Examiner on page 8 of the Office Action continues to allege that:

  > It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the PCP descriptors of Venkatarajan with the alignment methods of Zhu in sequence data analysis because all the claimed elements were known, in the prior art, as shown above. Further, one skill in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.

However, in addition to neither of the references describing, teaching, or suggesting the manner of defining PCP motifs as recited in claim 1, the following further shows that a

combination of Venkatarajan and Zhu do not establish a prima facie case of obviousness. For example, Zhu operates using pattern recognition on a multiple sequence alignment based on a pre-created or a selected macro. If a proposed modification would change the principle of operation of the prior art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (C.C.P.A. 1959).

Using the PCP descriptors of Venkatarajan with the alignment methods of Zhu as suggested by the Examiner in order to define PCP motifs according to the present invention would completely change the principle of operation of the process of Zhu. For example, Zhu only operates using pattern recognition on a multiple sequence alignment based on a pre-created or selected macro. Contrary to Zhu, the present invention as described in claim 1 defines PCP motifs using an algorithm as recited in claim 1 (e.g., including, for example, detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved according to at least one eigenvector). To modify Zhu (with the PCP descriptors of Venkatarajan) to obtain defined PCP motifs according to the definition algorithm of claim 1, would completely change the pattern recognition process of Masia. In other words, the proposed modification would change the principle of operation of the Zhu (i.e., the Masia pattern recognition process), and as such, the teachings of the references are not sufficient to render the claims *prima facie* obvious.

In other words, and contrary to the Examiner's remarks in the Office Action and as reproduced above, there is significant change in the functions of the cited references if combined as suggested by the Examiner. Such a combination thereof cannot be said to yield nothing more than predictable results.

The same or similar comments apply to claim 12, as well as the dependent claims which include the limitations of claim 1 or claim 12.

In view of the above information, for example, it is respectfully requested that the rejection under 35 U.S.C. §103(a) be withdrawn.

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the paper(s), as described hereinabove, are being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to the Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of February, 2008, at 2:25 pm (Central Time).

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